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Notes

Cycloaddition of *N*-Iminothiazolium Ylides with Acetylenic Dipolarophiles. Formation of Pyrazoles[1]

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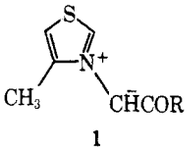
The cycloaddition of ylides derived from suitable heterocycles[2] with acetylenic dipolarophiles provides a convenient method of annelation of a second ring. We have shown[3] recently that in the reaction of the thiazolium ylide **1** with acetylenic dipolarophiles, the initial cycloadduct **2** underwent ready transformation to the 1*H*-pyrrolo[2,1-*c*][1,4]thiazine **3**. The reaction of the corresponding *N*-imino ylide **4** (R = H) with dimethyl acetylenedicarboxylate has been reported[4] to give the 7,9a-dihydrothiazolo[3,2-*b*][1,2]diazepine (**7**, R^1 = $COOCH_3$), a 1:2 adduct whose structure was assigned on the basis of spectral data. However, we have now found that although the data indicate that a 1:2 adduct was formed, rearrangement had occurred during the reaction and the product is the pyrazole **6**.



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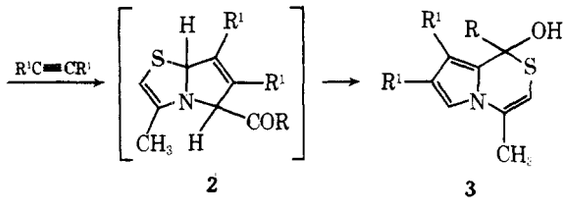
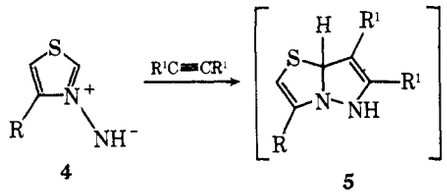
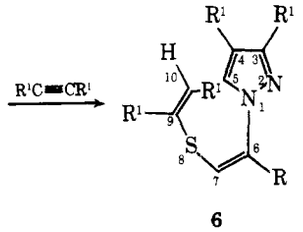


2 **3**

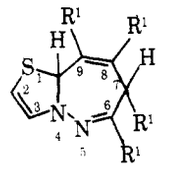


4 **5**



a, R = H; R^1 = $COOCH_3$
b, R = CH_3; R^1 = $COOCH_3$
c, R = CH_3; R^1 = COPh

6



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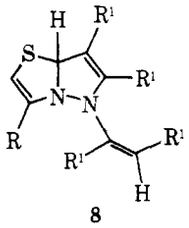

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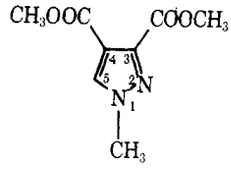

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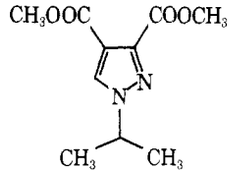

10

The ylide **4** (R = H, CH_3), generated in situ from the corresponding 3-aminothiazolium mesitylsulfonate[4] and NEt_3 (1 equiv) in DMF at room temperature, reacted readily with dimethyl acetylenedicarboxylate (2 equiv). After quenching the reaction from **4** (R = H) with ice–water and purification of the separated product by chromatography on silica gel, colorless needles of the pyrazole **6a** were obtained. Analytical and mass spectral data established the 1:2 composition of this product, and the ^1H NMR (100 MHz) data (Experimental Section) are consistent with this structure. These data are in agreement with those reported earlier for **7** but, rather than being definitive for structure **7**, they are also consistent with both structures **6a** and **8**. In terms of structure **7**, the observed coupling constant (8.0 Hz) between H_2 and H_3 is too large for these protons in a thiazoline ring, this coupling constant normally being ca. 5 Hz.[5] Similarly the chemical shift δ 8.08 of the proton assigned to the bridgehead H_{9a} is at too low a field compared to those observed for protons in an analogous environment.[3] However, structure **6a** readily accommodates the chemical shifts at δ 8.08, 7.02, 6.18, and 6.10 by protons at positions 5, 6, 7, and 10, respectively. The coupling constant $J_{6,7}$ = 8.0 Hz is consistent with maintaining a cis stereochemistry in the intermediate vinyl sulfide formed by fission of the C–S bond in **5**. The chemical shift of H_5 at δ 8.08 is also in agreement with that observed (δ 7.88) for H_5 in dimethyl 1-methylpyrazole-3,4-dicarboxylate (**9**) synthesized[6] from *N*-methylsydnone and dimethyl acetylenedicarboxylate.

^{13}C NMR data[7] provided decisive evidence in support of structure **6** (Table I). The absence of a resonance assignable to an sp^3 bridgehead carbon atom excludes structures **7** and **8**, and the seven sp^2 carbon atoms observed are readily accounted for by structure **6**. Off-resonance decoupling established that four of these carbon atoms bear a hydrogen atom,

Table I. ^{13}C Chemical Shift Assignments (ppm) for Some Pyrazole Derivatives ($CDCl_3$)

Structure	Carbon atoms at positions 3	4	5	6	7	9	10	CO	Ester CH_3
6a	145.8	115.9	134.2	124.5	111.0	114.4	118.9	165.4	53.2
								163.8	52.7
								161.6	52.1
6b[a]	147.0	115.7	133.0	135.0	109.7	144.2	118.0	165.7	53.2
								164.1	52.7
								162.2	52.1
								161.9	
9[b]	143.5	115.1	135.5					162.2	52.5
									51.7

[a] C_6CH_3, 21.4 ppm. [b] NCH_3, 39.8 ppm.

and the chemical shifts of C_9 and C_{10} were found to be analogous to those of the related carbon atoms in bis(2-carboethoxyvinyl) sulfide which occurred at 147.8 and 116.3 ppm, respectively.

From the reaction of the ylide **4** (R = CH_3) with dimethyl acetylenedicarboxylate, in addition to the pyrazole **6b** a small amount of a nonseparable mixture (mp 105–109 °C) of **6b** and an isomeric product was isolated. NMR data of the mixture indicated that the isomer (ν_{CO} 1725, 1745 cm^{-1}) was present to ca. 10% of the total mixture. The ^1H NMR spectrum of **6b** showed chemical shifts consistent with the assigned structure as were the ^{13}C chemical shifts shown in Table I. A very small splitting (<1 Hz) of the C_6CH_3 and H_7 indicated the cis relationship of these two groups to each other in **6b** and also in the isomeric product. This suggests that the two isomers are most likely cis–trans isomers formed in the addition of the intermediate vinyl sulfide obtained from **5** by fission of the C–S bond to a second molecule of dimethyl acetylenedicarboxylate, such additions usually occurring in a trans fashion.[8] Dibenzoylacetylene also reacted with **4** (R = CH_3) giving the pyrazole **6c.**

Chemical evidence for structure **6b** was obtained by desulfurization with Raney nickel (W-2). Methyl 1-isopropylpyrazole-3,4-dicarboxylate (**10**) was isolated by preparative TLC (silica gel, benzene–acetone, 9:1) as a colorless oil and the NMR spectrum of the crude reaction mixture also showed the presence of an equivalent amount of dimethyl succinate [δ 3.68 (s, 6, $COOCH_3$), 2.61 (s, 4, CH_2)].

Experimental Section[9]

Preparation of the *N*-Aminothiazolium Salts. An ice-cold solution of the thiazole (20 mmol) in dry dichloromethane (15 mL) was treated dropwise with a solution of *O*-mesitylenesulfonylhydroxylamine (20 mmol) in dichloromethane (15 mL). After stirring for 10 min at room temperature anhydrous ether (10 mL) was added. On cooling colorless needles of 3-aminothiazolium mesitylenesulfonate, mp 93–95 °C, the precursor of **4** (R = H), and 3-amino-4-methylthiazolium mesitylenesulfonate, mp 128 °C, the precursor of **4** (R = CH_3), separated.[4]

Reaction of the *N*-Iminothiazolium Ylides with Activated Acetylenes. A stirred solution (0 °C) of the appropriate thiazolium salt and 2 equiv of the acetylene in dry dimethylformamide was treated dropwise with an equimolar amount of triethylamine. After stirring for 4 h at room temperature, the mixture was poured into ice–water and the precipitated solid was collected, dried (**6a** was chromatographed on silica gel), and recrystallized from the appropriate solvent.

The pyrazole **6a** crystallized as colorless needles from ethanol: mp 120–121 °C (lit.[4] mp 122–124 °C), 32%; IR (KBr) 1710, 1730, 1740 cm^{-1} (CO); λ_{max} (CH_3OH) 315 nm (log ϵ 4.29), 230 sh (4.0); NMR (100 MHz, $CDCl_3$) δ 8.08 (s, 1, H_5), 7.02 (AB d, 1, J = 8.0 Hz, H_6), 6.18 (AB d, 1, J = 8.0 Hz, H_7), 6.10 (s, 1, H_{10}), 3.92, 3.84, 3.80, 3.68 (each s, 12, $COOCH_3$); M^+·384 (17).

Anal. Calcd for $C_{15}H_{16}N_2O_8S$: C, 46.87; H, 4.19; N, 7.29. Found: C, 46.77; H, 4.11; N, 7.22.

The pyrazole **6b** formed colorless needles from ethanol: mp 118 °C, 40%; IR (KBr) 1725, 1735 cm^{-1} (CO); λ_{max} (CH_3OH) 317 nm (log ϵ 4.16), 225 sh (4.0); NMR (100 MHz, $CDCl_3$) δ 8.08 (s, 1, H_5), 6.04 (broad s, 2, H_7, H_{10}), 3.93, 3.86, 3.82, 3.70 (each s, 12, $COOCH_3$), 2.35 (d, 3, $J \simeq 1$ Hz, CH_3); M^+·398 (20).

Anal. Calcd for $C_{16}H_{18}N_2O_8S$: C, 48.23; H, 4.55; N, 7.03. Found: C, 48.24; H, 4.49; N, 6.98.

The mother liquor from the crystallization of **6b** was concentrated, giving a yellow, crystalline product shown to be a mixture of **6b** and an isomer: mp 105–109 °C; NMR (100 MHz, $CDCl_3$) δ 8.27, 8.08 (each s, 1, H_5), 6.04 (broad d, 2, H_7 and H_{10}), 3.94, 3.86, 3.82, 3.76, 3.70 (each s, 12, $COOCH_3$), 2.35, 2.31 (each d, 3, $J \simeq 1$ Hz, C_6CH_3).

Anal. Calcd for $C_{16}H_{18}N_2O_8S$: C, 48.23; H, 4.55; N, 7.03. Found: C, 48.29; H, 4.51; N, 7.03.

The pyrazole **6c** formed cream prisms from dichloromethane–pentane: mp 150 °C, 29%; IR (KBr) 1655, 1675 cm^{-1} (CO); NMR (60 MHz, $CDCl_3$) δ 8.17–7.22 (m, 22, aromatic, H_5 and H_{10}), 6.13 (broad s, 1, H_7), 2.35 (broad s, 3, CH_3); M^+·582 (4).

Anal. Calcd for $C_{36}H_{26}N_2SO_4$: C, 74.23; H, 4.47; N, 4.81. Found: C, 73.95; H, 4.55; N, 4.81.

Desulfurization of Pyrazole 6b with Raney Nickel. The pyrazole (0.4 g, 1 mmol), freshly prepared Raney nickel[10] (4 g), and ethanol (15 mL) were refluxed with stirring for 2.5 h and filtered. The filtrate was stripped of solvent. Methyl 1-isopropylpyrazole-3,4-dicarboxylate (**10**) was isolated from the crude product by PLC (silica gel, benzene–acetone, 9:1) as a colorless oil: IR (film) 1750, 1740, 1725 cm^{-1} (CO); NMR (60 MHz, $CDCl_3$) δ 7.93 (s, 1, H_5), 4.58 (septet, 7, >CH), 3.95 (s, 3, $COOCH_3$), 3.83 (s, 3, $COOCH_3$), 1.53 (d, 6, J = 6.7 Hz, CH_3); M^+·226 (23).

Registry No.—**4** (R = H), 59046-20-7; **4** (R = CH_3), 61544-00-1; **6a,** 61558-10-9; **6b,** 61544-01-2; **6b** isomer, 61544-02-3; **6c,** 61544-03-4; **9,** 22050-80-2; **10,** 61544-04-5; thiazole, 288-47-1; 4-methylthiazole, 693-95-8; *O*-mesitylenesulfonylhydroxylamine, 36016-40-7; 3-aminothiazolium mesitylenesulfonate, 52197-73-6; 3-amino-4-methylthiazolium mesitylenesulfonate, 61544-06-7; dimethly acetylenedicarboxylate, 762-42-5; dibenzoylacetylene, 1087-09-8.

References and Notes

(1) Partial support of this work by USPHS Research Grant CA 08495, National Cancer Institute, is gratefully acknowledged.
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(9) Spectral characterizations were carried out on the following instrumentation: IR, Perkin-Elmer Model 337 infrared spectrophotometer; UV, Cary Model 14 spectrophotometer; NMR, Varian T-60A and HA-100 spectrometers; mass spectra, Hitachi Perkin-Elmer RMU-6E spectrometer. The mass spectral data were obtained at 70 eV using the direct insertion probe and a source temperature of ca. 100 °C. All evaporations were done under reduced pressure on a rotatory evaporator and melting points were determined in capillaries. Analyses were by Instranal Inc., Rensselaer, N.Y.
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